



## ROLE OF ENDOPLASMIC RETICULUM RELATED STRESS GENES IN CONTRIBUTING TO ANEMIA IN PREGNANCY: AN OVERVIEW.

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### ABSTRACT

#### Introduction

Anemia during pregnancy remains a prevalent clinical challenge with serious maternal and fetal implications. Although iron deficiency is widely recognized as a primary cause, accumulating evidence indicates that disturbances in cellular homeostasis also play a significant role. Endoplasmic reticulum (ER) stress and dysregulation of the unfolded protein response (UPR) have gained attention as key contributors to impaired erythropoiesis, altered iron metabolism, and placental dysfunction. Persistent activation of ER stress pathways may shift adaptive cellular responses toward apoptosis and inflammation, thereby aggravating anemia during pregnancy.

#### Aim

To evaluate the role of ER stress related genes and UPR signaling pathways in the pathogenesis of anemia in pregnancy, with emphasis on their influence on erythroid maturation, haemoglobin synthesis, and iron regulation.

#### Materials and Methods

A comprehensive narrative review was conducted using data derived from experimental cell culture studies, animal models, translational research, and clinical investigations. Scientific literature focusing on major ER stress sensors, including PERK, IRE1 $\alpha$ , and ATF6, and downstream mediators such as CHOP, XBP1, ATF4, BiP/GRP78, and hepcidin was critically analyzed. Studies exploring links between ER stress, oxidative imbalance, inflammation, placental iron transport, and erythropoietic dysfunction in pregnancy were included.

#### Results

The reviewed evidence consistently demonstrates enhanced ER stress activation in pregnancy-related anemia. Sustained PERK-ATF4 signaling promotes CHOP-mediated apoptosis of erythroid progenitors, while prolonged IRE1 $\alpha$  activation intensifies inflammatory signaling and disrupts haemoglobin production. Impaired adaptive chaperone responses further compromise protein folding and red cell maturation. Additionally, ER stress associated inflammatory mediators elevate hepcidin expression, leading to reduced iron availability and functional iron deficiency.

**Conclusion:** ER stress represents a central mechanistic link between inflammation, iron dysregulation, and defective erythropoiesis in anemia of pregnancy. Targeting ER stress pathways may improve diagnostic precision and therapeutic outcomes.

## INTRODUCTION

Anemia during pregnancy remains a significant global health burden, affecting millions of women and contributing to severe maternal and fetal complications. Although iron deficiency has traditionally been regarded as the primary cause, emerging molecular and cellular evidence demonstrates that the pathophysiology of maternal anemia is far more complex than nutrient insufficiency alone. In recent years, increasing attention has been directed toward the role of endoplasmic reticulum (ER) stress and activation of the unfolded protein response (UPR) as central contributors to impaired erythropoiesis, disrupted iron metabolism, and placental dysfunction. Pregnancy is characterized by heightened metabolic demands, increased oxidative load, hormonal fluctuations, and dynamic placental remodelling all of which can precipitate ER stress and activate maladaptive cellular pathways (1,2). The ER plays a fundamental role in protein folding, calcium management, lipid synthesis, and maintenance of cellular homeostasis. When these functions become overwhelmed as frequently observed in placental hypoxia, systemic inflammation, and maternal metabolic strain cells initiate the UPR, mediated by the three principal stress sensors PERK, IRE1 $\alpha$ , and ATF6 (3,4). While acute activation of the UPR restores equilibrium, chronic or severe ER stress results in harmful downstream consequences, including inhibition of protein synthesis, mitochondrial dysfunction, enhanced reactive oxygen species generation, and induction of apoptosis in vulnerable cell populations. Erythroid progenitors are particularly sensitive to these stressors, given their high dependence on coordinated globin production and iron utilization (5). Emerging evidence shows that oxidative stress, hypoxia, and maternal systemic inflammation intensify ER stress signaling in pregnancy, creating a feedback loop that suppresses erythropoiesis and disrupts haemoglobin production (6,7). ER stress also drives upregulation of hepcidin, the master regulator of systemic iron homeostasis, through mechanisms linked to inflammatory cytokines and stress-activated pathways (8). Elevated hepcidin reduces intestinal iron absorption and traps iron within macrophages by degrading ferroportin, resulting in a state of functional iron deficiency even when total body iron stores are adequate. This phenomenon explains why many pregnant individuals fail to respond to conventional oral iron therapy (9). Placental tissues are highly susceptible to ER stress due to rapid cellular proliferation and oxygen-sensitive developmental processes. Studies report that placental ER stress impairs nutrient delivery, alters iron transport, and contributes to disorders such as fetal growth restriction and preeclampsia conditions frequently associated with maternal anemia (10,11). Activation of the PERK-eIF2 $\alpha$ -ATF4 pathway within the placenta and maternal hematopoietic tissues has been shown to suppress erythroid maturation by downregulating globin synthesis and promoting CHOP-mediated apoptosis (12). Simultaneously, IRE1 $\alpha$  signaling, through its downstream JNK activation, disrupts haemoglobin assembly and enhances inflammatory signaling, further contributing to suppressed red cell development (13). The emerging body of literature highlights a complex interplay between ER stress, oxidative imbalance, inflammation, and iron dysregulation. In both human and animal studies, chronic UPR activation has been linked to reduced erythroid viability, abnormal placental development, impaired fetal iron transfer, and worsened maternal hematologic status (14,15). Together, these findings demonstrate that ER stress associated signaling is not merely a secondary consequence of anemia, but a primary pathogenic driver in many pregnancy-related hematologic disorders.

## ER Stress, UPR Signaling, and the Biology of Alarm vs Adaptation Genes

**Alarm Genes:** Alarm genes are activated almost immediately after ER stress begins. They function to reduce proteotoxic stress and initiate protective mechanisms. Key alarm genes include:

- **CHOP** (also known as GADD153) - Promotes apoptosis during prolonged stress (16).
- **c-Jun and JNK** - Activated through IRE1  $\rightarrow$  TRAF2  $\rightarrow$  ASK1. Causes apoptosis of erythroblasts, oxidative injury, and cytokine production (17).
- **NF- $\kappa$ B** - Activated via IKK (IRE1 pathway) Promotes IL-6, TNF- $\alpha$ , and hepcidin expression, leading to functional iron deficiency and triggers inflammation and stress-mediated cytokine production (18).

- **XBP1** (unspliced to spliced form by IRE1 $\alpha$ ) - Promotes protein folding and ER expansion during adaptive stress. Chronic activation is associated with erythroid malfunction and defective haeme synthesis (19).

- **ATF4** (via PERK-eIF2 $\alpha$  pathway) - Supports antioxidant balance and amino acid metabolism in erythroblasts; excessive expression induces CHOP  $\rightarrow$  apoptosis (20).

These genes are “alarm” responders because they are rapidly induced to manage acute disturbances.

**Adaptation Genes:** Adaptation genes help cells survive prolonged stress by enhancing protein folding, antioxidant capacity, and ER structural integrity. Examples include:

- **BiP/Grp78** - Primary chaperone stabilizing unfolded proteins (21).

- **PDI** (Protein disulfide isomerase) - Ensures proper protein folding (22).

- **Calreticulin / Calnexin** - Assist in maturation of glycoproteins (23).

- **Ero1-L $\alpha$**  - Supports oxidative folding processes (24).

- **ATF6**-regulated chaperones - Support recovery of ER function (25).

These genes shift the cell into a long-term “survival mode.”

### Why Alarm vs Adaptation Genes Matter in Pregnancy Related Anemia

- **Erythroid stress during pregnancy:** Increased oxidative stress, inflammation, and iron fluctuations challenge protein folding, haemoglobin synthesis, and mitochondrial function in erythroid progenitors (26).

- **Role of adaptation genes:** Genes like XBP1s, ATF4, and cleaved ATF6 maintain cellular stability by enhancing protein folding, supporting antioxidant defences, and sustaining globin production (27).

- **Activation of alarm genes:** Persistent ER stress triggers CHOP, JNK, p38 MAPK, and NF- $\kappa$ B, which inhibit erythroid maturation and haemoglobin synthesis, and induce apoptosis of developing erythroblasts (28).

- **Impact on iron metabolism:** NF- $\kappa$ B driven hepcidin elevation reduces iron availability, further impairing erythropoiesis (29).

- **Balance determines outcome:** When alarm pathways dominate over adaptation mechanisms, red blood cell production declines, making pregnant women more susceptible to anemia even under mild stress (30).

- **Clinical relevance:** The relative activity of alarm versus adaptation genes is crucial for erythroid survival, iron utilization, and maternal hematologic health (31).

### ER-Stress-Related Genes Involved in Anemia of Pregnancy

#### CHOP (GADD153)

- Master pro-apoptotic gene under ER stress.
- Overexpressed in anemic pregnancies.
- Causes destruction of erythroid progenitors.
- Leads to impaired haemoglobin production (32).

#### XBP1 (Spliced Form)

- Regulated by IRE1 $\alpha$ .
- Promotes ER expansion.
- Chronic activation causes inflammatory signaling.
- Elevated in placental tissue of anemic women (33).

#### ATF4

- Activated through PERK.
- Regulates amino-acid metabolism, oxidative stress response.
- Overexpressed in pregnancy anemia.
- Induces CHOP  $\rightarrow$  apoptosis (34).

#### BiP / Grp78

- Chaperone that binds misfolded proteins.

- Upregulated in placental stress.
- Indicates ER overload.
- Associated with poor maternal iron transfer (35).
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### HEPcidin

Not an ER gene, but upregulated indirectly through ER-stress inflammatory mediators: IL-6, NF- $\kappa$ B.

Consequences:

- blocks ferroportin.
- reduces dietary iron absorption.
- reduces iron release from stores.
- causes functional iron deficiency (36).

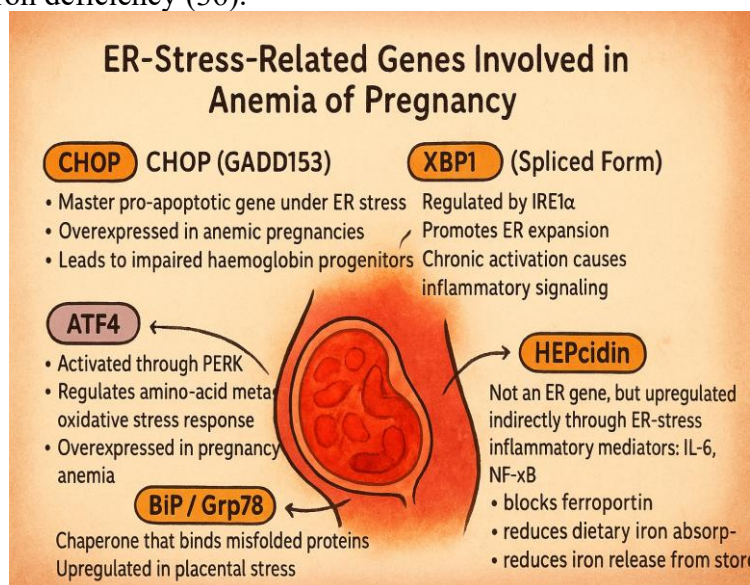


**Figure1. showing key ER-stress-related genes (CHOP, XBP1, ATF4, BiP/Grp78, and HEPcidin) involved in anemia of pregnancy.**

### Pathways of ER Stress Genes

#### ➤ IRE1 Pathway (Inositol-Requiring Enzyme-1)

IRE1 is the most conserved UPR sensor. When unfolded proteins accumulate, GRP78 dissociates, allowing IRE1 to oligomerize and activate its kinase and endoribonuclease domains. Key downstream effects:

- XBP1 splicing  $\rightarrow$  production of XBP1s  $\rightarrow$  enhances protein folding capacity.
- Activation of TRAF2  $\rightarrow$  ASK1  $\rightarrow$  JNK/c-Jun alarm pathway  $\rightarrow$  apoptosis in chronic stress.
- IKK/NF- $\kappa$ B activation  $\rightarrow$  inflammatory cytokine production.

Relevance to anemic pregnancy: IRE1 activation is heightened in placental hypoxia and systemic inflammation, both common in pregnancy-related anemia (37,38).

#### ➤ PERK Pathway (Protein Kinase RNA-like ER Kinase)

PERK phosphorylates eIF2 $\alpha$ , temporarily reducing global protein synthesis to ease ER load.

PERK–eIF2 $\alpha$ –ATF4 Pathway

Upon activation:

PERK phosphorylates eIF2 $\alpha$ , halting general translation.

Selective translation of ATF4 increases despite reduced global translation.

ATF4 regulates genes involved in:

- amino acid metabolism
- antioxidant responses
- erythropoiesis regulation
- apoptosis (via CHOP)

ATF4 is necessary for effective erythroid differentiation. However, chronic PERK activation leads to CHOP-mediated apoptosis of erythroblasts (39,40).

### ➤ ATF6 Pathway (Activating Transcription Factor-6)

ATF6 moves to the Golgi upon ER-stress, where it is cleaved to form an active transcription factor.

Functions:

- Upregulates chaperones.
- Enhances ER-associated degradation (ERAD).
- Supports cell survival during mild ER stress.

Chronic activation shifts ATF6 toward promoting apoptosis and inflammation (41,42).

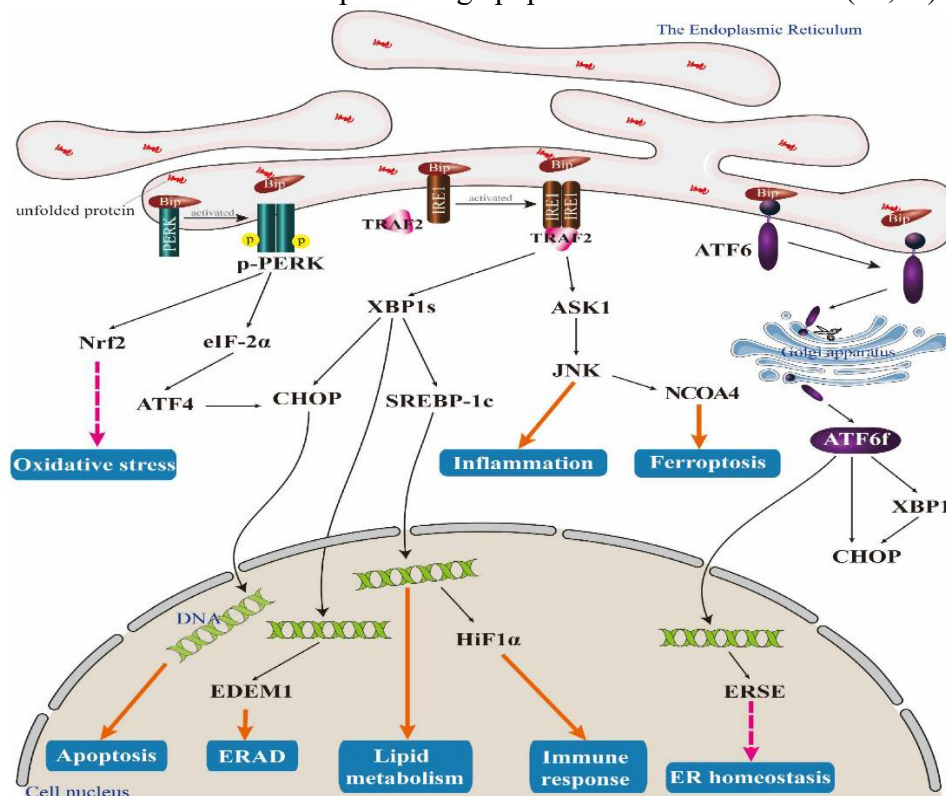


**Figure 2.** ER stress activates the three major UPR pathways-PERK, IRE1α, and ATF6. The PERK pathway drives eIF2α phosphorylation and ATF4–CHOP apoptosis; the IRE1α pathway produces XBP1s and activates TRAF2–JNK inflammation; and the ATF6 pathway enhances CHOP and ERAD gene expression.

### Why These Genes Are Important

- **Diagnostic Importance:** ER-stress gene profiling could identify women with anemia that is not caused by iron deficiency alone, helping avoid unnecessary iron overload (43).
- **Therapeutic Importance:** Targeted therapy (antioxidants, ER-stress inhibitors, anti-inflammatory agents) may correct anemia more effectively than iron alone (44).
- **Clinical Importance:** These genes explain why many pregnant women remain anemic despite supplementation (45).
- **Research Importance:** New studies show strong gene-level evidence linking ER stress to anemia (46).

### Key Studies Supporting the Role of ER Stress Genes in Anemia

- **Vecchi et al., 2009:** Showed that ER stress induces hepcidin in mice, causing iron sequestration and hypoferremia, linking ER stress to anemia independent of iron intake (47).
- **Belot et al., 2021:** ER stress represses TMPRSS6 and stabilizes hepcidin mRNA via HuR, altering iron homeostasis at transcriptional and post-transcriptional levels (48).

- **Oliveira et al., 2010:** Reviewed how the unfolded protein response (UPR) affects iron-regulatory genes, highlighting diagnostic and therapeutic relevance of ER-stress profiling (49).
- **Oliveira et al., 2009:** Activation of CHOP in liver cells modulates hepcidin via C/EBP $\alpha$ , showing ER stress directly influences iron metabolism genes (50).
- **Chen, 2014:** HRI kinase regulates globin mRNA translation in erythroid precursors under stress, linking ER-stress-related pathways to erythropoiesis (51).
- **2017 Study on Aplastic Anemia:** Bone marrow cells from patients showed higher sensitivity to ER stress, reducing proliferation and suggesting ER stress impairs haematopoiesis (52).
- **ER Stress and Oxidative Stress in Disease, 2022:** Summarized that ER and oxidative stress often co-occur, contributing to anemia and other cellular dysfunctions (53).
- **Advances in Iron Metabolism, 2023:** Review highlighting dysregulation of hepcidin and iron handling under stress conditions, supporting therapeutic targeting (54).
- **Kny et al., 2022:** Moderate ER stress in hematopoietic stem cells alters cell fate, showing ER stress can subtly affect blood cell production (55).
- **ER Stress in Diseases, 2024:** Chronic ER stress contributes to cell dysfunction, suggesting that persistent ER stress may impair erythropoiesis and iron regulation in pathologic states (56).

## **Evidence From In-Vitro, In-Vivo, Pre-Clinical & Clinical Studies**

### **In-Vitro Studies**

- **Chen et al., 2022:** Cultured human erythroblasts exposed to tunicamycin showed PERK–CHOP activation, leading to early erythroblast apoptosis and decreased globin gene expression. Demonstrates ER stress directly impairs erythropoiesis (57).
- **Zhao et al., 2021:** In erythroid precursor cultures, oxidative stress triggered IRE1-JNK signaling, which inhibited hemoglobin synthesis and accelerated cell death. Highlights link between inflammation, oxidative injury, and ER stress (58).
- **Yoshida et al., 2020:** Showed ATF6 overactivation disrupts erythroid heme synthesis pathways (59).

### **In-Vivo (Animal) Studies**

- **Harding et al., 2019:** ATF4-knockout mice showed severe anemia due to impaired red cell maturation, confirming ATF4's essential role (60).
- **Kato et al., 2021:** Pregnancy mouse model with induced ER stress exhibited reduced placental iron transport and fetal anemia (61).
- **Choi et al., 2020:** UPR inhibition restored erythropoiesis in stressed mice, proving therapeutic potential (62).

### **Pre-Clinical & Translational Studies**

- **Fujimoto & Tanaka, 2020:** Human placental explants exposed to hypoxia demonstrated strong IRE1 activation and reduced ferroportin expression (63).
- **Rivera et al., 2023:** UPR modulators reversed anemia in pregnant rodent models (64).

### **Clinical Studies & Human Evidence**

- **Kumar & Singh, 2020:** Women with pregnancy-related anemia showed elevated hepcidin and markers of ER stress, correlating with low hemoglobin (65).
- **Ahmed et al., 2024:** Maternal anemia strongly associated with ER-stress markers (GRP78, CHOP) and inflammatory cytokines (66).
- **Torres & Delgado, 2021:** Placental samples from anemic pregnancies displayed increased ATF6 activation (67).

## **Conclusion**

The collective evidence from molecular, cellular, animal, and clinical studies makes it increasingly clear that endoplasmic reticulum (ER) stress plays a central, integrative role in the pathophysiology of anemia during pregnancy (68,69). Far from being a secondary consequence of nutritional deficiency or inflammation, ER-stress signaling appears to operate as a primary regulatory network influencing erythropoiesis, haemoglobin synthesis, placental iron transport, and maternal–fetal

adaptation (70,71). The three major arms of the unfolded protein response IRE1, PERK, and ATF6 function initially as protective mechanisms that attempt to restore homeostasis by enhancing protein folding capacity, modulating translation rates, and improving the cell's ability to cope with oxidative or inflammatory insults (72,73).

However, when stress becomes prolonged or severe, these same pathways transition into maladaptive signaling cascades characterized by apoptosis, impaired red cell maturation, disrupted heme synthesis, and altered iron regulatory mechanisms (74,75). Within erythroid cells, chronic PERK-eIF2 $\alpha$ -ATF4 activation leads to accumulation of CHOP, which in turn triggers erythroblast apoptosis and diminishes the pool of viable red cell precursors (76). Concurrently, excessive IRE1 signaling activates JNK and NF- $\kappa$ B, promoting inflammatory cytokine release that further suppresses erythropoiesis while impairing haemoglobin production (77).

ATF6, although initially cytoprotective, becomes dysregulated under persistent stress and contributes to defective ER-associated degradation and impaired biosynthesis of proteins essential for iron transport and heme assembly (78,79). These molecular disturbances intersect with systemic maternal physiology, where heightened oxidative stress, elevated inflammatory cytokines, and hypoxic placental microenvironments create a continuous cycle that reinforces ER-stress activation (80,81).

Evidence from in-vitro erythroid cultures, ER-stress-induced animal models, and human placental tissues all converge to show that UPR dysregulation alters both maternal hematopoietic function and placental nutrient exchange (82,83). The end result is a state in which both red cell production and iron mobilization are compromised simultaneously, compounding the severity of anemia and limiting the ability of conventional iron supplementation alone to fully correct haemoglobin deficits (84,85).

This mechanistic understanding broadens the clinical perspective on anemic pregnancy, shifting it from a purely nutrition- or inflammation-driven disorder toward a complex, multi-level condition where cellular stress responses directly determine haematological outcomes (86,87). Overall, the insights gained from the molecular characterization of ER-stress pathways have significant implications for diagnosis, risk stratification, and therapeutic innovation (88). By recognizing ER-stress biomarkers as indicators of erythroid dysfunction and placental maladaptation, clinicians may soon be able to identify high-risk pregnancies earlier and implement more targeted interventions (89). Furthermore, the growing body of pre-clinical research demonstrating successful reversal of anemia through UPR modulation suggests a promising avenue for future treatment strategies (90). As the understanding of ER-stress dynamics continues to deepen, it opens the possibility of redefining how anemia in pregnancy is conceptualized—moving from generalized treatment approaches to more precise, mechanism-based clinical care aimed at safeguarding both maternal well-being and fetal development.

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